

Review Article

Amiodaron in atrial fibrillation: post coronary artery bypass graft

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BACKGROUND: Atrial fibrillation (AF) is the most common complication following heart surgeries; it often occurs in patients after coronary artery bypass graft (CABG). The purpose of this review is to categorize prophylaxes or treatment by administration of Amiodaron in patients with CABG.

DATA RESOURCES: We searched google scholar, pubmed, and Cochrane Library databases (the period 1970–2010) for articles on Amiodaron in CABG and cardiac surgery. A total of 1 561 articles were identified, and 30 articles met the criteria and were enrolled in this review.

RESULTS: Most studies supported Amiodarone for prophylaxi purpose in patients who were performed with CABG; few papers supported Amiodaron as a drug for treating CABG. The prophylaxis can decrease the incidence rate of AF in CABG, but if it uses as a treatment, the side effect of Amiodaron will decrease because all of the patients will not get Amiodarone. In the other hand use of Amiodarone as a treatment does not influence the length of hospital stay significantly but these kinds of study are so few.

CONCLUSION: No appropriate therapeutic method has been defined for AF. At present, the common way of treating AF following cardiac surgery is mainly based on prophylaxis in medical books and references.

KEY WORDS: Pulmonary aspiration; Lateral position; Semi-lateral position

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INTRODUCTION

Atrial fibrillation (AF) is the most common complication and arrhythmia following cardiac surgeries, which occurs in about one third of patients after coronary artery bypass graft (CABG). This arrhythmia is often benign and transient, but can cause hemodynamic disorders, serious complications including cerebral apoplexy, and increase in the length of hospitalization.^[1–3]

No appropriate treatment method has yet been defined for AF after surgery. To decrease appearance of this complication, more attention has been paid to prophylactic methods in recent decades. Generally, preventing serious complications, decreasing length of hospitalization and as a result, decreasing treatment costs can be regarded as the main reasons for prophylactic treatment in

preventing AF appearance after cardiac surgeries.

During recent years, application of antiarrhythmic drugs has been studied for AF prophylaxis after surgery. Amiodarone is an antiarrhythmic drug, which can be regarded as one of the effective drugs for AF after surgery. The studies conducted on Amiodarone have considered its prophylactic effects in preventing from AF after surgery.

DEFINITION OF ATRIAL FIBRILLATION

AF is a supraventricular tachyarrhythmia diagnosed through irregular atrial activities and disappearance of atria mechanical function. In electrocardiogram (ECG), AF appears as quick vibrating waves replaced by P-waves and often accompanied by quick and irregular ventricular

response. AF may occur in isolation or along with other arrhythmias (atrial flutter or atrial tachycardia, in most cases).^[3]

EPIDEMIOLOGY

Annually, about 700 000 patients undergo open cardiac surgery in US.^[4] AF appears following CABG in about 11%–40%.^[5] This rate varies according to definitions and diagnosis methods of AF.^[6] In spite of advancement of surgery, anesthesia and care methods after surgery, it has not decreased.^[7]

PROGNOSIS

Post-surgery AF is regarded as a benign and self-restricting complication^[6] and often occurs 1–5 days after cardiac surgery. The highest level of its manifestation is observed on the second day. More than 90% of patients suffering from AF without previous history of the disease, return to sinus rhythm within 6–8 weeks after surgery.^[8] AF is the most common reason of re-hospitalization following cardiac surgeries.^[6] AF is not accompanied by an increase in mortality during hospitalization,^[1] but it may increase risk of some complications in these patients including cerebral apoplexy, ventricular arrhythmia, chronic heart failure (CHF), infectious problems, digestive complications and renal insufficiency.^[1,9,10] Additionally, AF is accompanied by increasing the length of hospitalization and treatment costs.^[8]

PREDICTORS

Different studies have been conducted to determine AF risk factors following surgeries. They can be helpful in identifying AF pathophysiological mechanism and also making prevention and treatment of the complication more purposeful through identifying patients exposing to risk.

Old age is the only factor consistently accompanied by increasing of AF risk. AF predictors are listed in Table 1.^[1,11–15]

PATHOPHYSIOLOGY

The basis of AF manifestation mechanism after surgery is probably similar to that with no relation to surgery. However, few studies have been conducted regarding the electrophysiology basis of arrhythmia after surgery.

Pathophysiology suggested by Moe for AF includes reentry or automatic electrical discharge. Therefore, it is expected that conditions lead to the development of focal areas with automatic function or several short periods from reentry areas may result in atrial arrhythmia including fibrillation. Local refractoriness is the primary condition for AF manifestation. In a cardiac undergoing surgery, several factors may dispose the patient to AF through this mechanism. Enhanced power of sympathetic or vagal tone may decrease the AF developing threshold. Metabolic and chemical conditions including hypocalcaemia, hypokalemia and hypothyroidism may also play a role in development and continuation of AF. Lateral conditions of surgeries accompanied with high AF manifestation risk include myocardium ischemic damage during operation due to hypotension or insufficient cardio support, traumatic pericardia and myocardium, increase of atrial pressure resulting from decrease of left ventricle function following surgery and anesthesia, metabolic and chemical conditions and activation of autonomic reflex. The transient nature of AF after surgery is related to improvement of these metabolic or mechanical conditions.^[6,16,17]

PROPHYLAXIS

Considering the high prevalence of AF after cardiac surgeries, it is recommended to use prophylaxis treatment especially at the presence of risk factors.^[8]

Research demonstrated that antiarrhythmic drugs with controlling effect of β -adrenergic receptors (class II β -blockers, Sotalol and Amiodarone) are useful in prophylaxis. Those drugs, which do not generally control β receptors, are not effective in decreasing AF manifestation after surgeries. According to the evidences,

Table 1. AF predictors after heart surgery

Pre-operation factors	In-operation factors	Post-operation factors
Age over than 75 years	CABG along with valve improvement operation	ARDS
AF records	Pulmonary vein venting	Longer ventilation
Hypertension	Bicaval venous	Consumption of high doses of NSAIDs
Male	Cannulation	Atrial pace after surgery
Records of congestive heart failure	Cross-clamp longer time	
Anatomical distribution of coronary artery disease		
Sudden stop of β -blockers consumption		
Renal insufficiency		
COPD		
Weak function of left ventricle		
MI records		
Diabetes mellitus (DM)		

class II β -blockers have been introduced as the best prophylactic drug in decreasing AF after surgery.^[7]

The study done by Zebis et al,^[18] showed that post-operative prophylaxis with intravenous infusion (300 mg in 20-minute infusion) and followed by 600 mg oral Amiodarone significantly diminished the occurrence of postoperative AF.

In the other study, Zebis et al^[19] reported that administration of routine prophylactic Amiodarone (300 mg in 20-minute infusion followed by 600 mg oral Amiodarone for 5 days) decreased AF occurrence and the total costs of care up to 175€ per patient.

In another study, the authors gave infusion during the operation (300 mg Amiodarone for 1 hour total dose 20 mg/kg per day) and oral 600 mg from one day before surgery up to 7 days after surgery. It showed that prophylactic Amiodarone significantly reduced the incidence of AF in high-risk patients and also decreased length of stay in intensive care unit and hospital. The authors of this study believed that pre-operative Amiodarone prophylaxis is useful for prevention of AF in high-risk patients.^[20]

Daoud et al^[23] believed that only oral Amiodarone (600 mg per day) for 7 days then 200 mg per day up to discharge day was tolerable and significantly reduced the incidence of post-operative AF in patients who undergoing complex cardiac surgery. In another study, Guarnieri reported that low-dose intravenous Amiodarone (1 g over 24 hours, total 2 g of 48 hours) without loading dose which started 3 hours after surgery, reduced the incidence of AF after surgery, but did not have any significant effect on length of hospital stay.^[21]

TREATMENT

There is little information regarding drug treatment for AF after surgery in those patients not requiring immediate cardio restoration. Therefore, it is better to choose antiarrhythmic drug considering patient's specific details. For this purpose and considering some evidence, it is recommended to use Amiodarone to control rhythm especially in patients suffering from loss of left ventricle function.

In most protocols, the suggested duration of treatment with antiarrhythmic drugs is at least 4–6 weeks after surgery.^[21]

β -blockers, calcium channel controllers and also Amiodarone are introduced as effective drugs in controlling rate in patients suffering from AF.^[5]

The study showed that Amiodarone (150 mg infusion in 30 minute the 1 mg/kg for 6 hours then followed by 0.5 mg/kg for 18 hours, followed by oral up to discharge) given for treatment purpose after postoperative AF occurrence can decrease hospital stay beside prevention of side effect of prophylaxis in other patients.^[22]

DISCUSSION

Main advancements in cardiac surgery and also coronary arteries are not accompanied by main decrease in AF manifestation after surgery^[23] and AF has remained as one of the most common side effect of CABG.^[1] Seemingly, prevalence of this arrhythmia is increasing most probably resulting from increasing number of older patients undergoing cardiac surgery.^[6]

Research has shown that AF manifestation following cardiac surgery affects morbidity, hospitalization duration, and therapeutic costs.^[1] For this reason, arrhythmia attracted the attention of many researchers.

No appropriate therapeutic method has been defined for AF after surgery. During recent decades, most researches focused on preventive methods to decrease its manifestation.

Amiodarone can be used as one of effective drugs in treating AF after surgery. But, few comprehensive studies have verified its therapeutic effects following AF manifestation after cardiac surgeries. The studies focused on its prophylactic effects.

Amiodarone is a class III Vaughan-Williams antiarrhythmic drug and has some effects of Class I and II drugs as well as antiadrenergic effects.

Through obstructing potassium channels, the drug makes repolarization time longer, and therefore decreases membrane potential of myocardium cells. Amiodarone is a vasodilator of peripheral and coronary arteries. Amiodarone is prescribed as an oral or injection drug. When Amiodarone prescribed as vascular injection in 2.5–10 mg/kg doses, this may lead to heart rate decrease, persistence of peripheral arteries and contractive force of the left ventricle. Its oral doses are sufficient to control cardiac arrhythmia and do not lead to decrease of discharge fraction of the left ventricle even in patients with low EF. Oral Amiodarone is absorbed gradually and incompletely. Oral concentrations are maximized after 37 hours of one single dose. Drug concentration in myocardium is 10 to 15 times more than plasma.

Amiodarone is mainly metabolized in liver. Its plasma clearance is low and has a significant degree of renal excretion. Therefore, dose reduction is not required in patients suffering from renal diseases. Its effects appear after a few hours of vascular injection.

Main side effects of Amiodarone include bradycardia, cardio block, ventricle arrhythmia, interstitial pneumonia and liver poisoning. Exact mechanism of the drug effects on AF after surgery is not known. However, its effect is probably related to combination of antiadrenergic and class I and II antiarrhythmic effects.^[2]

It has been generally accepted that preventing manifestation of serious complications (including cerebral

apoplexy), decreasing hospitalization duration as well as therapeutic costs are regarded as main reasons to use prophylactic treatment to prevent AF manifestation following cardiac surgeries.^[24] Several studies have looked at the effects of different therapeutic methods on hospitalization duration and different results have been obtained.

A study introduced AF manifestation as the strongest predictive factor in increasing hospitalization duration following cardiac surgery. Old age, female, and African-American race occupy the next positions.^[25]

In the most comprehensive study conducted on oral Amiodarone, Daoud et al^[26] stated that consumption of oral Amiodarone for one week before surgery led to a 50% decrease of AF manifestation. Additionally, it resulted in decreasing hospitalization duration (1/4 days) and hospital costs. But, since most patients requiring CABG were in urgent condition and also considering probable pulmonary complications arising from Amiodarone consumption before surgery, application of this therapeutic diet has become difficult for all patients candidate for CABG. In their study on 570 cases of 70 years old or older patients, Aranki et al^[23] reported AF manifestation following cardiac surgery in 33% of the patients. They also stated that manifestation of the complication led to increase of hospitalization duration by 4.9 days.

Other studies conducted on prophylactic effects of Amiodarone against AF in patients with CABG surgery or those without any other surgeries including valve improvement reached different results considering effects of this therapeutic method on hospitalization duration after manifestation of the complication. They reported increase of hospitalization from 1 to 4.9 days.^[1,2,10,11,14,25]

In two meta-analyses conducted on Amiodarone, it was stated that effects of Amiodarone prophylaxis on decreasing hospitalization duration was not accompanied by considerable results.^[24] The results were similar to those of the present study about therapeutic effect of Amiodarone on hospitalization duration.

As observed, several studies conducted on AF after surgery and measures taken on prophylaxis had very different results in regards to AF manifestation and its effect of hospitalization duration. Possible reasons for these differences include: amiodarone dosage; treatment duration; amiodarone consumption method (injection, oral); CABG with/without cardiopulmonary bypass; accompanying of valve restoration operation with CABG; ways used in stopping and continuing β -blockers consumption near surgery.

Although prophylaxis significantly affects AF manifestation, reasons of less effect of prophylaxis on hospitalization duration is easily recognizable. General effects of this therapeutic method on hospitalization

duration depend on balance between decreasing the AF manifestation and as a result, decreasing the hospitalization duration on one hand and increasing of drug side effects on the other hand. Considering that less than half of the patients suffer from AF following cardiac surgery and an even smaller ratio of these patients suffer from long-term AF, most patients in whom no AF will be observed are exposed to side effects treatment due to being treated with prophylactic. This may finally lead to increase of hospitalization duration.

The conducted studies could not reject this probability that AF is a result of the observed side effects in these patients rather than their cause. Meanwhile, no relationship was observed between AF manifestation and inter-hospital mortality.^[1]

A relationship found between AF manifestation following cardiac surgery and cerebral apoplexy was introduced as one of the reasons for applying prophylactic treatment. A statistically powerful study cannot be conducted due to the low prevalence of cerebral apoplexy following cardiac surgeries. Meta-analysis of the available data provides no significant profitability against cerebral apoplexy. Also, there are several reasons confirming trivial effects of prophylactic method in treating AF on cerebral apoplexy.

As mentioned on hospitalization duration, just those patients will practically benefit from prophylactics who receive this treatment because most patients will not essentially suffer from AF. Finally, risk of AF-dependent infarction after surgery is very little.^[24]

The meta-analysis done by Crystal et al^[27] and published in *Circulation*, gave practical consideration that beta blockers were first-line medication for prevention of postoperative AF and Sotalol and Amiodarone were also effective and alternative.

Using biarterial pacing for 4 days shows that, it can reduce the incidence of AF after isolated CABG and can decrease complications and all can reduce ICU and hospital stay.^[28]

Some experts advised to use beta blockers early after all cardiac surgery, but there is a lack of evidence regarding to use routinely.^[29]

In recent years, some studies about n-3 Polyunsaturated fatty supplementations showed that it can significantly reduce the occurrence of AF in post cardiac surgery. Also it was safe and can administrate to all patients after CABG.^[30]

In conclusion, as mentioned, no appropriate therapeutic method has been defined for AF. At present, the common way of treating AF following cardiac surgery is mainly based on prophylaxis in medical books and references.

Considering that AF after surgery is often short-term, relatively asymptomatic and can be easily controlled, it can be stated that AF treatment after its manifestation

can be introduced as an appropriate way to deal with this complication rather than using pharmaceutical prophylaxis and as a result, confronting possible side effects of Amiodarone in most patients who will not suffer from AF as well as its costs imposed to patients and health system.

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REFERENCES

- Redle ID, Khurana S, Marzan R, McCullough PA, Stewart JR, Westreer DC, et al. Prophylactic oral amiodarone compared with placebo for prevention of atrial fibrillation after coronary artery bypass surgery. *Am Heart J* 1999; 138: 144–150.
- Brawnwald E. *Heart disease*. 7th Ed; 2005.
- Katzung BG. *Basic and clinical pharmacology*. 8th Ed. Mc Graw – Hill; 2001.
- Mason JW. Amiodaron. *N Engle J Med* 1987; 316: 455–466.
- Faniel R, Schoenfeld PH. Efficacy of i.v. amiodaron in converting rapid atrial fibrillation and flutter to sinus rhythm in intensive care patients. *Eur Heart J* 1983; 4: 180–185.
- Brugada P, Abdollah H, Heddle B, Wellens HJ. Results of a ventricular stimulation protocol using a maximum of 4 premature stimuli in patients without documented or suspected ventricular arrhythmias. *Am J Cardiol* 1983; 52: 1214–1218.
- Alboni P, Shanta N, Pirani R, Baggioni F, Scarfo S, Tomas AM. Effects of amiodaron on supraventricular tachycardia involving bypass tract. *Am J Cardiol* 1984; 53: 93–98.
- Rosenbavm MB, Chiale PA, Ryba D, Elizari MV. Control of tachyarrhythmias associated with Wolff-Parkinson-White syndrome by amiodarone hydrochloride. *Am J Cardiol* 1974; 34: 215–223.
- Andrivet P, Boubakri E, Dove PJ, Ngoc CV. A clinical study of amiodaron as a single oral dose in patients with recent – onset atrial tachyarrhythmia. *Eur Heart J* 1994; 15: 1396–1402.
- Escoubet B, Coumel P, Poirier JM, Maison-Blanche P, Jaillon P, Leclercq JF, et al. Suppression of arrhythmias within hours after a single dose of amiodaron and relation to plasma and myocardial concentrations. *Am J Cardiol* 1985; 55: 696–702.
- Fresco C, Proclemer A. Management of recent onset atrial fibrillation. *Eur Heart J* 1996; 17: 41–47.
- Falk RH. Proarrhythmia in patients treated for atrial fibrillation or flutter. *Ann Intern Med* 1992; 117: 141–150.
- Roden DM. Risk and benefits of antiarrhythmia therapy. *N Engl J Med* 1994; 331: 785–791.
- Singh SN, Fletcher RD, Fisher SG, Singh BN, Lewis HD, Deedwania PC, et al. Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmia. *N Engl J Med* 1995; 333: 77–82.
- Doral HC, Nul DR, Grancelli HO, Perrone SV, Bortman GR, Curiel R. Randomized trial of low dose amiodarone in severe congestive heart failure. *Lancet* 1994; 344: 493–498.
- Evans SJL, Myers M, Zaher C, Simonson J, Nalos P, Vavghn C, et al. High dose oral amiodarone loading: electro physiologic effects and clinical tolerance. *J Am Coll Cardiol* 1992; 19: 169–173.
- Peukhuriene K, Niemela M, Ylitalo A, Linnalouto M, Lilja M, Juronen J. Effectiveness of amiodarone as a single oral dose for recent – onset atrial fibrillation. *Am J Cardio* 2000; 85: 462.
- Zebis LR, Christensen TD, Thomsen HF, Mikkelsen MM, Folkersen L, Sorensen HT, et al. Practical regimen for Amiodarone use in preventing postoperative atrial fibrillation. *Ann Thorac Surg* 2007; 83: 1326–1331.
- Zebis LR, Christensen TD, Thomsen HF, Mikkelsen MM, Folkersen L, Sorensen HT, et al. Amiodarone coast effectiveness in preventing atrial fibrillation after coronary artery bypass graft surgery. *Ann Thorac Surg* 2008; 85: 28–33.
- Budeus M, Hennersdorf M, Perings S, Rohlen Sh, Schnitzler S, Felix O, et al. Amiodarone prophylaxis for atrial fibrillation of high risk patients after coronary bypass grafting: a prospective, double-blinded, placebo-controlled, randomized study. *Eur Heart J* 2006; 27: 1584–1591.
- Vietter-Ramus G, Veglio F, Marchisio U, Burzio P, Latini R. Efficacy and safety of short term intravenous amiodarone in supra ventricular tachyarrhythmia. *Int J cardial* 1992; 35: 77–85.
- Vahdati SS, Samadikhah J, Hakim SH, Azarfarin R, Ansarin M. Comparison of the length of hospital stay between the patients with atrial fibrillation treated with amiodarone and patients with normal sinus rhythm after coronary artery bypass graft. *J Cardiovasc Thorac Res* 2012; 4: 17–20.
- Guarnieri T, Nolan S, Gottlieb SO, Dudek A, Lowry DR. Intravenous amiodarone for the prevention of atrial fibrillation after open heart surgery: the Amiodarone Reduction in Coronary Heart (ARCH) trial. *J Am Coll Cardiol* 1999; 34: 343–347.
- Daoud EG, Strickberger SA, Man KC, Goyal R, Deeb GM, Bolling SF, et al. Preoperative amiodarone as prophylaxis against atrial fibrillation after open heart surgery. *N Engle J Med* 1997; 337: 1785.
- Butler J, Harriss DR, Sinclair M, Westaby S. Amiodarone prophylaxis for tachycardias after Coronary artery Surgery: a randomized, double blind, placebo Controlled trial. *Br Heart J* 1993; 70: 56–60.
- Hohnloser SH, Meinerz T, Dammacher T, Steiert K, Johnchen E, Zehender M, et al. Electrocardiographic and ant arrhythmic effects of intravenous amiodarone: results of prospective, placebo Controlled study. *Am Heart J* 1991; 121 (1 Pt 1): 89–95.
- Crystal E, Connolly SJ, Sleik K, Ginger TJ, Yusef S. Interventions on prevention of postoperative atrial fibrillation in patients undergoing heart surgery: A meta-analysis. *Circulation* 2002; 106: 75–80.
- Levy T, Fotopoulos G, Walker S, Rex S, Octave M, Paul V, et al. Randomized controlled study investigating the effect of biatrial pacing in prevention of atrial fibrillation after coronary artery bypass grafting. *Circulation* 2000; 102: 1382–1387.
- Hogue CW, Hyder ML. Atrial fibrillation after cardiac operation: risks, mechanisms, and treatment. *Ann Thorac Surg* 2000; 69: 300–306.
- Calò L, Bianconi L, Colivicchi F, Lamberti F, Loricchio ML, de Ruvo E, et al. N-3 Fatty acids for the prevention of atrial fibrillation after coronary artery bypass surgery: a randomized, controlled trial. *J Am Coll Cardiol* 2005; 45: 1723–1728.

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